5'- t ATCGAT tta CTA CTT GGA GGC AGT CAT -3' (SEQ ID NO: 13)

ClaI

Digest the PCR product with XbaI-ClaI, and ligate the resulting fragment into XbaI-ClaI-opened Z_{12}I-hGH-ss-XbaI. Perform DNA sequence to confirm cloning of the endostatin gene in frame with the secretory signal.

IN THE CLAIMS:

For the convenience of the Examiner, all claims being examined, whether or not amended, are presented below.

Please cancel, without prejudice, claims 4 and 15.

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1. **(Amended)** A cell containing

(a) a first genetic construct or pair of first genetic constructs encoding chimeric proteins comprising (i) at least one ligand-binding domain which can bind a selected ligand and (ii) a second protein domain, which is heterologous with respect to at least one of the ligand-binding domains, and

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(b) a target gene encoding an angiogenesis inhibitor under the expression control of a transcriptional control element responsive to binding of ligand to the ligand binding domain, wherein said angiogenesis inhibitor is angiostatin, and

wherein transcription of the target gene is regulated in a manner dependent on the expression of the chimeric protein and the presence of the ligand.

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2. **(Reiterated)** The cell of claim 1 wherein the chimeric proteins multimerize upon addition of ligand and wherein transcription of the target gene is responsive to the multimerization of the chimeric proteins.

3. **(Reiterated)** The cell of claim 1 wherein the ligand binding domain is selected from the group consisting of an immunophilin domain, a cyclophilin domain, a steroid hormone binding domain and an antibiotic binding domain.

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5. **(Amended)** The engineered cell of claim 1 in which the target gene encodes a peptide sequence of human origin.

14. **(Twice Amended)** A method for rendering a cell capable of regulatable expression of a target gene following exposure of said cell to a selected ligand, which method comprises introducing into said cell:

(a) a first genetic construct or pair of first genetic constructs encoding chimeric proteins comprising (i) at least one ligand-binding domain which can bind a selected ligand and (ii) a second protein domain, which is heterologous with respect to at least one of the ligand-binding domains, and

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(b) a target gene under the expression control of a transcriptional control element responsive to binding of ligand to the ligand binding domain,

wherein the target gene encodes an angiogenesis inhibitor, which angiogenesis inhibitor is angiostatin, and wherein the transcription of the target gene is regulated in a manner dependent on the expression of the chimeric protein and the presence of the ligand.

17. **(Twice Amended)** The method of claim 14 wherein the genetic constructs are introduced into a cell maintained in vitro.

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18. **(Twice Amended)** The method of claim 14 wherein the genetic constructs are introduced into a cell present within a host organism.

19. **(Reiterated)** The method of claim 14 wherein the chimeric proteins multimerize upon addition of ligand and wherein transcription of the target gene is responsive to the multimerization of the chimeric proteins.

20. **(Amended)** The method of claim 14 wherein the ligand binding domain is selected from the group consisting of an immunophilin domain, a cyclophilin domain, a steroid hormone binding domain and an antibiotic binding domain.

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24. **(Reiterated)** The method of claim 14, wherein at least one of (a) or (b) is introduced into said cell by a viral vector.

25. **(Reiterated)** The method of claim 24, wherein the viral vector is selected from the group consisting of adenovirus, adeno-associated virus, herpesvirus, and retrovirus.

26. **(Reiterated)** The method of claim 14, wherein the cell is a mammalian cell.

27. **(Reiterated)** The method of claim 26, wherein the mammalian cell is a human cell.

28. **(Reiterated)** The method of claim 14, wherein the cell is a cell type selected from the group consisting of neural, mesenchymal, cutaneous, mucosal, stromal, spleen, reticuloendothelial, epithelial, endothelial, kidney, gastrointestinal and pulmonary cells.

29. **(Reiterated)** The method of claim 14, wherein the genetic construct further comprises one or more selectable markers.

30. **(Reiterated)** The method of claim 29, wherein the selectable marker is selected from the group consisting of an antibiotic resistance gene and herpes simplex virus-thymidine kinase.

31. **(Reiterated)** The method of claim 14, wherein the target gene is a human gene.

32. **(Reiterated)** The method of claim 14, wherein the selected ligand binds the ligand-binding domain with a K_d value less than 10^{-6} M.

33. **(Reiterated)** The method of claim 14, wherein the selected ligand binds the ligand-binding domain with a K_d value less than 10^{-9} M.

34. **(Reiterated)** The method of claim 14, wherein the selected ligand is not a protein and wherein the selected ligand has a molecular weight less than 5 kDa.

35. **(Reiterated)** The method of claim 14, wherein the chimeric protein includes two or more ligand-binding domains having different ligand binding specificities.

36. **(Reiterated)** The method of claim 14, wherein at least one of the ligand-binding domains is from 50 to 350 amino acid residues in length.

37. **(Reiterated)** The method of claim 14, wherein said selected ligand is membrane permeable.

38. **(Reiterated)** The method of claim 14, wherein said selected ligand is orally active.

The amended claims are restated below to reflect changes with respect to the last filing.

1. **(Amended)** A cell containing

(a) a first genetic construct or pair of first genetic constructs encoding chimeric proteins comprising (i) at least one ligand-binding domain which can bind a selected ligand ~~to form a ligand-crosslinked protein complex including the chimeric protein~~ and (ii) a second protein domain, which is heterologous with respect to at least one of the ligand-binding domains, and

(b) a target gene encoding an angiogenesis inhibitor under the expression control of a transcriptional control element responsive to binding of ligand to the ligand binding domain, <u>wherein said angiogenesis inhibitor is angiostatin, and</u>

wherein transcription of the target gene is regulated in a manner dependent on the expression of the chimeric protein and the presence of the ligand.

5. **(Amended)** The engineered cell of claim 1 ~~or 4~~ in which the target gene encodes a peptide sequence of human origin.

14. **(Twice Amended)** A method for rendering a cell capable of regulatable expression of a target gene following exposure of said cell to a selected ligand, which method comprises introducing into said cell:

(a) a first genetic construct or pair of first genetic constructs encoding chimeric proteins comprising (i) at least one ligand-binding domain which can bind a selected ligand ~~to form a ligand- corsslinked complex including the chimeric protein~~ and (ii) a second protein domain, which is heterologous with respect to at least one of the ligand-binding domains, and

(b) a target gene under the expression control of a transcriptional control element responsive to binding of ligand to the ligand binding domain,

wherein the target gene encodes an angiogenesis inhibitor, which angiogenesis inhibitor is angiostatin ~~or a tumor specific antigen~~, and wherein the transcription of the target gene is regulated in a manner dependent on the expression of the chimeric protein and the presence of the ligand.

17. **(Twice Amended)** The method of claim 14 ~~or 16~~ wherein the genetic constructs are introduced into a cell maintained in vitro.

18. **(Twice Amended)** The method of claim 14 ~~or 16~~ wherein the genetic constructs are introduced into a cell present within a host organism.

20. **(Amended)** The method of claim 14 ~~or 16~~ wherein the ligand binding domain is selected from the group consisting of an immunophilin domain, a cyclophilin domain, a steroid hormone binding domain and an antibiotic binding domain.

REMARKS

Claims 1-38 constitute the pending claims in the present application. Applicants cancel, without prejudice, claims 4 and 15. Applicants respectfully request reconsideration in view of the following remarks. Issues raised by the Examiner will be addressed below in the order they appear in the prior Office Action.